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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,298	02/08/2000	JUNKO YAMAMOTO	1422-411P	1749

2292 7590 02/28/2006

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,298	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21,23,24,26-28,30 and 44-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,23,24,26-28,30 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Upon careful reconsideration of the application in view of Applicants' IDS received subsequent to the Final Rejection, the finality of the rejection of the last Office action is withdrawn in view of the references cited therein.

Preliminary Remark

All rejections/objections hereto not reiterated is(are) considered withdrawn.

Claim Rejections - 35 USC § 103

Rejections, New Grounds – Necessitated by IDS

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 21, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al. (U.S. Patent No. 5,693,517, issued December 2, 1997; IDS reference # AA) in view of Kaiser et al. (U.S. Patent No. 5,843,669, issued December 1, 1998, filed November 29, 1996).

Gelfand et al. disclose an RT –PCR reaction (column 6, lines 60-64), wherein in the "RT" (reverse transcriptase) reaction, artisans disclose that the use of hydroxymethyl dUTP or 7-deaza-dGTP in generating a first strand cDNA (column 20, line 56 through column 21, line 5).

Gelfand et al. do not disclose that the nucleotide analogs are employed in the subsequent PCR reaction.

Kaiser et al. disclose a method of amplifying (via PCR) employing 7-Deaza-dATP and 7-Deaza-dGTP) (column 24, lines 29-26; column 183, lines 1-9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Gelfand et al. and Kaiser et al. to arrive at the claimed invention for the following reasons.

The technique of RT-PCR is a well-known process of amplifying a sample in a species, wherein the target nucleic acid to be amplified is an RNA or mRNA.

Gelfand et al. seeks to improve the traditional RT-PCR reaction by reducing the possibility of cross-contamination which carries over from the reverse-transcription reaction to the subsequent amplification reaction (PCR):

"Due to the enormous amplification possible with the PCR process, small levels of DNA carryover from samples with high DNA levels, positive control templates or from previous amplification can result in PCR product, even in the absence of purposefully added template DNA" (column 13, lines 6-11)

Gelfand et al. disclose several embodiments drawn to suppressing this cross-contamination, wherein one of the explicitly disclosed embodiment is drawn to the method of incorporating nucleotide analogs, such as hydroxymethyl dUTP (herein HmdUTP) (column 20, lines 56-59) instead of dTTP in the reverse transcription reaction. The artisans state that this substitution into "cDNA effectively lowers the denaturation temperature of both reverse transcribed product [the 1sts strand cDNA produced] and the PCR duplex DNA product, in comparison to the denaturation temperature of the homologous thymine containing DNA." (column 20, line 63 through column 21, line 1."

Gelfand et al., in the context of this disclosure also suggests that, "[o]ther modified nucleoside triphosphates capable of effecting the Tm of DNA product (e.g., c7dGTP, 7 deaza-

deoxyguanosine 5'-triphosphate [7-deaza dGTP] or α-phosphorothioate dNTPs)..." (column 21, lines 1-4).

Hence, given such a disclosure, one of ordinary skill in the art would have been clearly motivated to employ any of the known nucleoside analogs which are known to lower the melting temperature of a double stranded nucleic acid, when incorporated, particularly, the 7-deaza dGTP and HmdUTP, in the reverse transcription reaction.

The motivation to combine elements which are directed for the same purposes is also supported in *In re Kerkhoven* (*see* MPEP 2144.06), wherein the court expressed the following:

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

With regard to the combination of the teachings of Gelfand et al. with that of Kaiser et al., that is, substituting the PCR reaction of the RT-PCR reaction disclosed by Gelfand et al., such motivation is clearly present in view of the disclosure provided for by Kaiser et al.:

"The 7-deaza purine analogs (7-deaza-dATP and 7-deaza-dGTP) serve to ***destabilize regions of secondary structure by weakening the intrastrand stacking of multiple adjacent purines. This effect can allow amplification of nucleic acids that, with the use of natural dNTPs, are resistant to amplification because of strong secondary structure***" (column 183, lines 1-8).

Hence, one of ordinary skill in the art at the time the invention was made would have been motivated to improve the PCR reaction of Gelfand et al., with the 7-deza nucleotide analogs of

Kaiser et al, because by doing so, one of ordinary skill in the art would have been able to amplify target nucleic acids having a strong secondary structure.

It is also of note that while Gelfand et al. are not explicit in disclosing that HmdUTP and 7-deaza GTP be used in the PCR reaction, the artisans appear to consider this possibility as well:

> "Incorporation of HmdUTP into cDNA effectively lowers the denaturation temperature of both reverse transcribed product [or 1st strand cDNA] **and** the PCR product..." (column 20, lines 63-66)

"Methods are provided for both non-homogeneous and homogenous RT/PCR assays. The term, 'homogeneous' as used herein refers to a two-step single addition reaction for reverse transcription and amplification of an RNA target. By homogeneous it is meant that following the reverse transcription step, there is **no need to open the reaction vessel or otherwise adjust reaction components prior to the amplification step."** (column 6, lines 39-46).

Hence, a homogeneous RT-PCR reaction involving the above-disclosed modified nucleoside analogs would also certainly be incorporated in the PCR reaction.

With regard to claim 44, drawn to a method of reverse transcription and amplification involving 7-deaza dGTP and 7-deaza dATP, it is determined that in view of the disclosure provided for by Kaiser et al. who employ these two nucleoside analogs, one of ordinary skill in the art would have had the motivation to employ the two nucleoside analogs for the same motivation as discussed above.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at such combination as the incorporation of nucleotide analogs during primer extension as already been demonstrated to be feasible by Kaiser et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 23, 24, 26-28, 30, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al. (U.S. Patent No. 5,693,517, issued December 2, 1997; IDS reference # AA) in view of Kaiser et al. (U.S. Patent No. 5,843,669, issued December 1, 1998, filed November 29, 1996) and Pergolizzi et al. (U.S. Patent No. 5,658,764, issued August 19, 1997).

Gelfand et al. disclose an RT –PCR reaction (column 6, lines 60-64), wherein in the "RT" (reverse transcriptase) reaction, artisans disclose that the use of hydroxymethyl dUTP or 7-deaza-dGTP in generating a first strand cDNA (column 20, line 56 through column 21, line 5).

Gelfand et al. do not disclose that the nucleotide analogs are employed in the subsequent PCR reaction.

Gelfand et al., in their method, employ a compound which lowers Tm of double stranded nucleic acids.

Kaiser et al. disclose a method of amplifying (via PCR) employing 7-Deaza-dATP and 7-Deaza-dGTP) (column 24, lines 29-26; column 183, lines 1-9).

Perfolizzi et al. disclose a method of amplifying a target nucleic acid by a polymerase chain reaction (PCR), wherein the reaction employs nucleoside analog 7-deaza dGTP as well as DMSO (dimethyl sulfoxide) (see column 8, lines 43-52).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Gelfand et al., Kaiser et al., and Perfolizzi et al., thereby arriving at the claimed invention for the following reasons.

The technique of RT-PCR is a well-known process of amplifying a sample in a species, wherein the target nucleic acid to be amplified is an RNA or mRNA.

Gelfand et al. seeks to improve the traditional RT-PCR reaction by reducing the possibility of cross-contamination which carries over from the reverse-transcription reaction to the subsequent amplification reaction (PCR):

"Due to the enormous amplification possible with the PCR process, small levels of DNA carryover from samples with high DNA levels, positive control templates or from previous amplification can result in PCR product, even in the absence of purposefully added template DNA" (column 13, lines 6-11)

Gelfand et al. disclose several embodiments drawn to suppressing this cross-contamination, wherein one of the explicitly disclosed embodiment is drawn to the method of incorporating nucleotide analogs, such as hydroxymethyl dUTP (herein HmdUTP) (column 20, lines 56-59) instead of dTTP in the reverse transcription reaction. The artisans state that this substitution into "cDNA effectively lowers the denaturation temperature of both reverse transcribed product [the 1sts strand cDNA produced] and the PCR duplex DNA product, in comparison to the denaturation temperature of the homologous thymine containing DNA." (column 20, line 63 through column 21, line 1."

Gelfand et al., in the context of this disclosure also suggests that, "[o]ther modified nucleoside triphosphates capable of effecting the Tm of DNA product (e.g., c7dGTP, 7 deaza-deoxyguanosine 5'-triphosphate [7-deaza dGTP] or α-phosphorothioate dNTPs)..." (column 21, lines 1-4).

Hence, given such a disclosure, one of ordinary skill in the art would have been clearly motivated to employ any of the known nucleoside analogs which are known to lower the melting temperature of a double stranded nucleic acid, when incorporated, particularly, the 7-deaza dGTP and HmdUTP, in the reverse transcription reaction.

The motivation to combine elements which are directed for the same purposes is also supported in *In re Kerkhoven* (*see* MPEP 2144.06), wherein the court expressed the following:

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

With regard to the combination of the teachings of Gelfand et al. with that of Kaiser et al., that is, substituting the PCR reaction of the RT-PCR reaction disclosed by Gelfand et al., such motivation is clearly present in view of the disclosure provided for by Kaiser et al.:

"The 7-deaza purine analogs (7-deaza-dATP and 7-deaza-dGTP) serve to ***destabilize regions of secondary structure by weakening the intrastrand stacking of multiple adjacent purines. This effect can allow amplification of nucleic acids that, with the use of natural dNTPs, are resistant to amplification because of strong secondary structure***" (column 183, lines 1-8).

Hence, one of ordinary skill in the art at the time the invention was made would have been motivated to improve the PCR reaction of Gelfand et al., with the 7-deza nucleotide analogs of Kaiser et al, because by doing so, one of ordinary skill in the art would have been able to amplify target nucleic acids having a strong secondary structure.

It is also of note that while Gelfand et al. are not explicit in disclosing that HmdUTP and 7-deaza GTP be used in the PCR reaction, the artisans appear to consider this possibility as well:

> "Incorporation of HmdUTP into cDNA effectively lowers the denaturation temperature of both reverse transcribed product [or 1st strand cDNA] **and** the PCR product..." (column 20, lines 63-66)

"Methods are provided for both non-homogeneous and homogenous RT/PCR assays. The term, 'homogeneous' as used herein refers to a two-step single addition reaction for reverse transcription and amplification of an RNA target. By homogeneous it is meant that following the reverse transcription step, there is **no need to open the reaction vessel or otherwise adjust reaction components prior to the amplification step."** (column 6, lines 39-46).

Hence, a homogeneous RT-PCR reaction involving the above-disclosed modified nucleoside analogs would also certainly be incorporated in the PCR reaction.

With regard to claims 45 and 46, drawn to a method of reverse transcription and amplification involving 7-deaza dGTP and 7-deaza dATP, it is determined that in view of the disclosure provided for by Kaiser et al. who employ these two nucleoside analogs, one of ordinary skill in the art would have had the motivation to employ the two nucleoside analogs for the same motivation as discussed above.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at such combination as the incorporation of nucleotide analogs during primer extension as already been demonstrated to be feasible by Kaiser et al.

Finally, the motivation to combine a compound which lowers the Tm temperature of a double stranded nucleic acid during PCR reaction, is explicitly provided for by Pergolizzi et al.:

> "The inability of PCR-based methods to detect GC-rich sequence has hindered the development of an assay for other conditions." (column 3, lines 1-3)

Such difficulty, as recognized in the art, arises from the strong hydrogen bonds formed between the base, "G: and its complementary base "C" in the GC rich region.

Pergolizzi et al., in their attempt to overcome this difficulty, disclose a method which employs reagents which render the double-strand nucleic acid, single stranded for amplification.

Pergolizzi et al. explicitly disclose a preferred embodiment employing 7-deaza GTP and 10% DMSO in an amplification reaction.

Hence, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the reagents of Pergolizzi et al. with the teachings of Gelfand et al. and Kaiser et al. for the advantage of facilitating melting (*i.e.,* become single stranded) of any double stranded nucleic acids, such as DMSO, in an amplification reaction.

As Pergolizzi et al. already couples 7-deaza GTP with DMSO in a PCR reaction, one of ordinary skill in the art would have had a clear expectation of success at combining the PCR reaction of Pergolizzi et al. with the teachings of Gelfand et al. and Kaiser et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
2/24/2006

YOUNG J. KIM
PATENT EXAMINER

yjk